INE INSTITUTE OF NUTRITIONAL ENDOCRINOLOGY

Digestion: Endocrinology of Appetite

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Overall Control of Appetite

- ✓Brain centers
- ✓Neuropeptides
- ✓Insulin
- ✓Adipose hormones
- ✓Other hormones

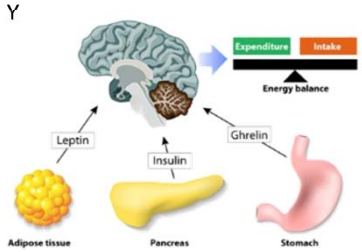
Brain Centers That Control Appetite

- ✓Hypothalamus
- ✓Brainstem
- ✓Nucleus accumbens
- ✓Ventral pallidum
- ✓Mesolimbic dopamine system (VTA NAc)
- ✓Other reward centers

Neuropeptide Control of Appetite

Neuropeptides regulate energy homeostasis.

- ➢Neuropeptide Y
- ➢Leptin
- ➢Orexin-A (hypocretin-1)
- ➢Orexin-B (hypocretin-2)



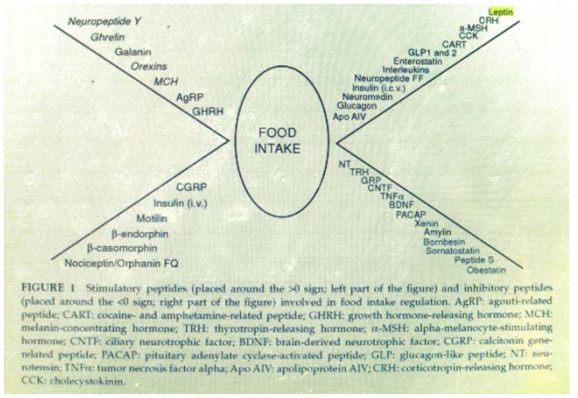


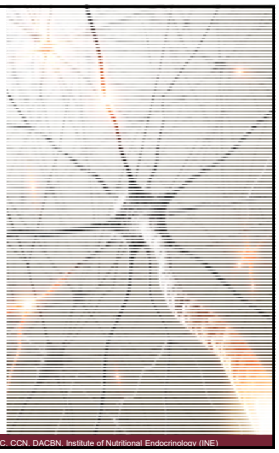
FIGURE 1 Stimulatory peptides (placed around the >0 sign; left part of the figure) and inhibitory peptides (placed around the <0 sign; right part of the figure) involved in food intake regulation. AgRP: agouti-related peptide; CART: cocaine- and amphetamine-related peptide; GHRH: growth hormone-releasing hormone; MCH: melanin-concentrating hormone; TRH: thyrotropin-releasing hormone; α-MSH: alpha-melanocyte-stimulating hormone; CNTF: ciliary neurotrophic factor; BDNF: brain-derived neurotrophic factor; CGRP: calcitonin gene-related peptide; PACAP: pituitary adenylate cyclase-activated peptide; GLP: glucagon-like peptide; NT: neurotensin; TNFα: tumor necrosis factor alpha; Apo AIV: apolipoprotein AIV; CRH: corticotropin-releasing hormone; CCK: cholecystokinin.

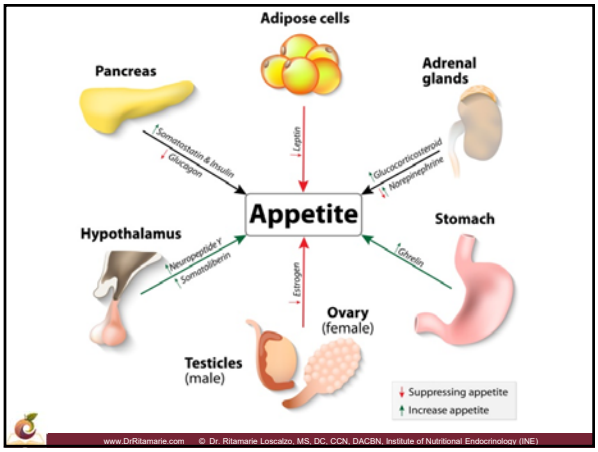
Appetite and Body Weight by Tim C Kirkham

Hormonal Control of Appetite

- ✓ Insulin
- ✓ Glucagon
- ✓ Leptin
- ✓ Ghrelin
- ✓ Other hormones synthesized by adipose tissue
- ✓ Gut hormones

These reflect the long-term nutritional status of the body and are able to influence neural circuits.





Appetite Hormones

Hormones	Appetite Related Functions
Amylin	• Delays gastric emptying • Lowers blood glucose
CCK (cholecystokinin)	• Suppresses hunger and signals satiety • Inhibits gastric emptying • Stimulated gallbladder secretion • Influences PYY release • Stimulated by fat and protein
CRF (corticotropin-releasing factor)	• Reduces appetite
Dopamine	• Reinforces pleasure from food • Contributes to cravings
Ghrelin	• Triggers hunger • Increases preference for fatty and sweet foods • Increases gastric motility

Appetite Hormones

Hormones	Appetite Related Functions
GIP (glucose-dependent insulinotropic polypeptide)	• Stimulates insulin release while eating; diabetics become resistant to GIP
GLP-1 (glucagon like peptide 1)	• Slows gastric emptying • Promoted insulin release and inhibits glucagon • Suppresses appetite
Glucagon	• Increases satiety
Insulin	• Lowers blood glucose • Stimulated glycogen synthesis • Stimulates fat synthesis and storage
Leptin	• Decreases food intake • Regulates metabolism
Adiponectin	• Enhances fatty acid oxidation and reduces triglycerides • Stimulates glucose uptake by muscle • Inhibits glucose production by the liver • Decreases blood glucose levels • Decreases appetite

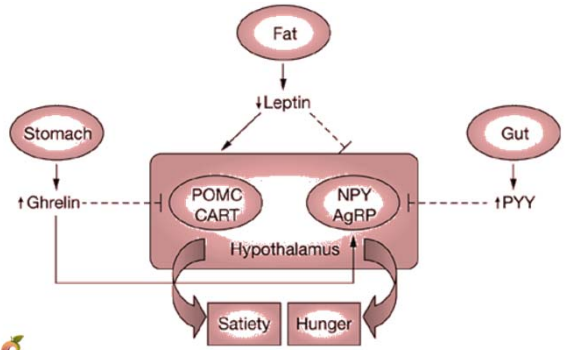
Appetite Hormones

Hormones	Appetite Related Functions
NPY (neuropeptide Y)	• Stimulates appetite
OXM (oxyntomodulin)	• Inhibits ghrelin secretion • Suppresses appetite • Slows gastric emptying • Stimulates insulin release after carbohydrate intake
PP (pancreatic polypeptide)	• Slows gastric emptying
PYY (peptide YY)	• Slows gastric emptying • Suppresses appetite • Stimulates satiety (levels are highest 90 minutes after starting a meal)
Serotonin	• Decrease linked with carbohydrate cravings • Provides calm feeling after eating sugar
Orexin	• Promotes eating beyond satiety

Other Hormones that Influence Appetite

Hormones	Appetite Related Functions
Melatonin	• Sleep deprivation decreases melatonin production, which decreases leptin and increases ghrelin production
Sex hormones	• Estrogen suppresses appetite • Imbalance estrogen /progesterone ratio can trigger intense food cravings
Cortisol	• Sustained high levels can lead to intense cravings and binge eating

Appetite Regulation



Leptin

- ✓ Secreted by the fat cells – the white adipose tissue
- ✓ Signals the hypothalamus and pancreas "we are full"
- ✓ Hypothalamus response is to turn off appetite
- ✓ Pancreas response is to stop producing insulin
- ✓ Has a 24-hour circadian rhythm and is controlled by eating
- ✓ Pancreas and hypothalamus become leptin resistant

Normal Leptin Function

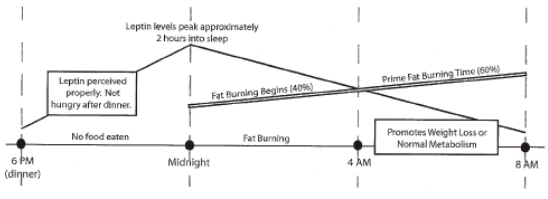
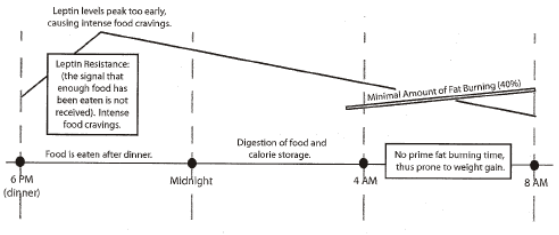


Chart from: Richards BJ. *Mastering Leptin.* Minneapolis: Wellness Resources Books, 2004

Leptin Resistance



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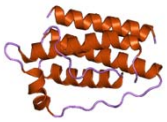
Things That Disrupt Leptin Signaling

- ✓High carbohydrate meal in the morning
- ✓Eating too frequently
- ✓Insufficient sleep
- ✓Insulin resistance
- ✓Fungicide tolylfluanid and other endocrine disruptors
- ✓Bisphenol A (BPA)

Leptin Modulation

Increase:
- Insulin
- Cortisone
- Estrogens



Decrease:
- Adrenaline
- Male hormones
- Growth hormone

Optimizing Leptin and Insulin

- ✓Avoid eating after dinner
- ✓Stick to three meals a day; no snacking
- ✓Allow five to six hours between meals
- ✓Avoid large meals
- ✓Eat slowly
- ✓Eat a breakfast containing protein
- ✓Reduce intake of starchy carbohydrates

Meal Timing and Leptin

- ✓ **Avoid snacking:** Prolonged insulin curves or more frequent insulin spikes plus decreased leptin promote obesity
- ✓ **Maintain ideal body weight:** Obesity increases insulin resistance
- ✓ **Avoid eating at night:** Late eating increases insulin and decreases growth hormone and leptin
- ✓ **Avoid high-carbohydrate breakfasts:** Morning carb overdoses cause a premature spike in leptin and food cravings
- ✓ **Eat protein within an hour of waking:** Morning protein consumption promotes growth hormone and regulates insulin

Ghrelin

- ✓Secreted by cells in the stomach wall
- ✓Eating suppresses ghrelin
- ✓An empty stomach secretes ghrelin freely
- ✓Ghrelin stimulates appetite
- ✓Ghrelin is a potent stimulator of growth hormone
- ✓Waiting to eat until very hungry and stomach is empty stimulates fat burning and muscle sparing

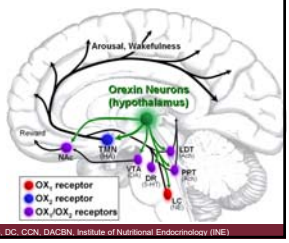
Resistin

- ✓ Peptide secreted by fat cells
- ✓ Discovered in 1995
- ✓ Named for ability to resist insulin
- ✓ Links obesity, insulin resistance, and diabetes
- ✓ AKA adipose tissue-specific secretory factor (ADSF)
- ✓ Cysteine-rich adipose-derived peptide hormone encoded by the RETN gene
- ✓ Increases insulin resistance as more fat cells accumulate around the waist
- ✓ These fat cells secrete leptin

http://www.drritamarie.com/go/ResistinFunctionalRoles

Orexin

- ✓ A neuropeptide released by the posterior lateral hypothalamus
- ✓ Linked to wakefulness and sleep, appetite regulation, and the motivation of sexual and addictive behaviors
- ✓ Often described as "a hormone in the brain with the effects of adrenaline and testosterone in one"
- ✓ Plays a key role in promoting eating and appetite and seems to work to signal "eat more," beyond satiety
- ✓ Two variations identified



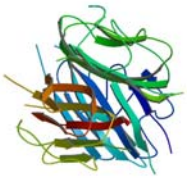
Neuropeptide Y (NPY)

- ✓ Most abundant neuropeptide in the brain
- ✓ Possibly stronger than ghrelin at stimulating appetite
- ✓ Rats given an NPY will crave sugar water over sex
- ✓ The primary trigger is calorie restriction and low leptin
- ✓ Primary job is to delay the feeling of fullness
- ✓ Tells the body where and how to store extra calories as either fat or muscle
- ✓ High levels will cause less fullness and calories will preferentially be stored as fat

Neuropeptide Y (NPY) Interactions

- ✓ Leptin inhibits NPY
- ✓ Hypothalamic NPY stimulates the secretion of insulin and cortisol and shifts metabolism to favor synthesis and storage of fat
- ✓ Weight loss caused by caloric restriction ("dieting") stimulates NPY release in the periventricular nucleus

Adiponectin



- ✓ 244-amino-acid-long polypeptide
- ✓ Produced by adipose
- ✓ Increases metabolic rate
- ✓ Plays an important role in the energetic capacity of skeletal muscle
- ✓ Counteracts inflammation and insulin resistance
- ✓ Important for weight loss
- ✓ Increases insulin sensitivity and effects insulin levels
- ✓ A deficiency makes it almost impossible to melt fat and stay thin - helps the body use fat to fuel muscle cells

Adiponectin Causes Weight Loss Without Affecting Appetite

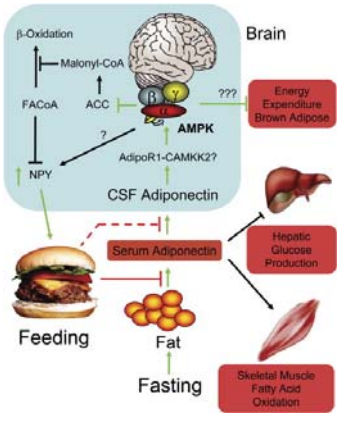
- ✓ Receptors in the hypothalamus and some forms enter the cerebrospinal fluid
- ✓ Enhances fatty acid oxidation in muscle and liver, thus reduces triglyceride content in these tissues
- ✓ Stimulates glucose uptake by skeletal and cardiac muscle and inhibits glucose production by the liver
- ✓ Decreases blood glucose levels
- ✓ Needed to turn fat into energy - helps the body use fat to fuel muscle cells

Food and Adiponectin

- ✓ Daily intake of **fish or omega-3** supplementation increased adiponectin levels by 14-60%
- ✓ **Weight loss with low-calorie diet plus exercise** increased adiponectin levels in the range of 18-48%
- ✓ A 60-115% increase in adiponectin levels with **fiber supplementation**
- ✓ **High-carbohydrate meals** associated with lower adiponectin
- ✓ **Extracts of sweet potatoes** have been reported to increase levels

Diet and Adiponectin

- ✓ **Magnesium** associated with higher adiponectin
- ✓ **Coffee** associated with high adiponectin and low leptin
- ✓ Moderate **alcohol** intake is associated with higher adiponectin concentrations
- ✓ **Intermittent fasting** can increase adiponectin levels
- ✓ **Sleep can** increase adiponectin levels
- ✓ **Ayurvedic combination**
  - ➢ Betel - *Piper* betle
  - ➢ *Dolichos biflorus*



Adiponectin and Inflammation

✓ **Study In Mice:**

- Mice given TNF-alpha, which caused the release of inflammatory cytokines
- Injecting with adiponectin reversed the effects of the cytokines and inflammation

Effects of Adiponectin

- ✓ Decreases gluconeogenesis
- ✓ Increases glucose uptake
- ✓ Increases β-oxidation
- ✓ Increases triglyceride clearance
- ✓ Protection from endothelial dysfunction
- ✓ Improves insulin sensitivity
- ✓ Promotes weight loss
- ✓ Controls energy metabolism
- ✓ Reduces TNF alpha

Adiponectin Connections

- ✓ Lower levels associated with ADHD in adults
- ✓ Increased in rheumatoid arthritis
- ✓ Exercise-induced release of adiponectin increased hippocampal growth and led to antidepressive symptoms in mice

Adiponectin and Fats

- ✓ **10 week study with 17 healthy subjects**
  - ➢ Increased omega-3 intake and decreased omega-6 intake
  - ➢ Result: Significant reductions in TNF-alpha and low-density lipoprotein-cholesterol along with increased adiponectin

Nutritional intervention to reduce the n-6/n-3 fatty acid ratio increases adiponectin concentration and fatty acid oxidation in healthy subjects. Eur J Clin Nutrition. 2007.

- ✓ **Adiponectin as a marker for metabolic syndrome**

Int J Clin Exp Med. 2014. Adiponectin and visfatin may serve as diagnosis markers for metabolic syndrome in Uygur population.

Resources and References

- ✓ http://www.drritamarie.com/go/AppetiteControl
- ✓ http://www.drritamarie.com/go/NeuropeptidesFoodIntake
- ✓ http://www.drritamarie.com/go/OrexinHypocretin
- ✓ http://www.drritamarie.com/go/AWeightyMatter
- ✓ http://www.drritamarie.com/go/PharmacologicalManagementOfAppetite
- ✓ http://www.drritamarie.com/go/HypothalamicAppetiteRegulation
- ✓ http://www.drritamarie.com/go/HormonalRegulatorsOfAppetite
- ✓ http://www.drritamarie.com/go/AppetiteRegulation
- ✓ http://www.drritamarie.com/go/BrainRewardPathways
- ✓ http://www.drritamarie.com/go/PMID22387882
- ✓ http://www.drritamarie.com/go/BPAasObesogen

Resources and References

- ✓ http://www.drritamarie.com/go/ShortSleepDuration
- ✓ http://www.drritamarie.com/go/LeptinLevelsSleepDuration
- ✓ http://www.drritamarie.com/go/AdiponectinCausesWeightLoss
- ✓ http://www.drritamarie.com/go/RoleOfAdiponectin
- ✓ http://www.drritamarie.com/go/OpposingEffectsOfAdiponectin
- ✓ http://www.drritamarie.com/go/EffectOfDietOnAdiponectin
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- ✓ http://www.drritamarie.com/go/EatingForPleasureOrCalories